Biological/Immunological Considerations Moving Toward a 3-Month Contraceptive Dapivirine Ring

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Nothing to disclose.

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Target product: 90-day vaginal ring for pregnancy and HIV prevention

MTN
microbicide trials network

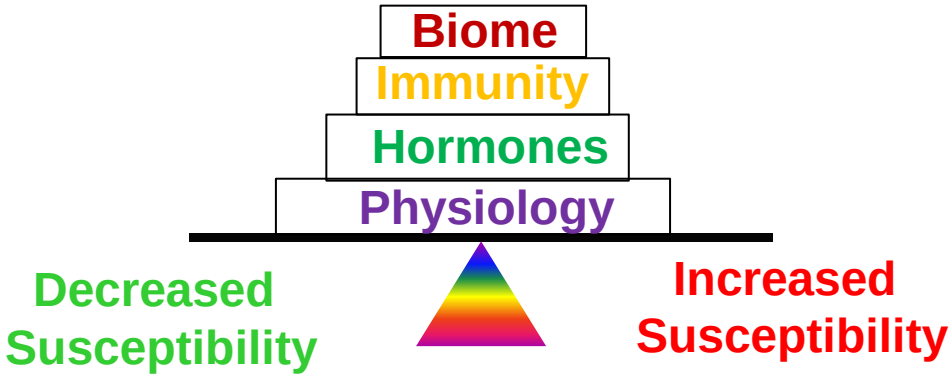
Microbicide
+
Contraceptive

International Partnership for Microbicides

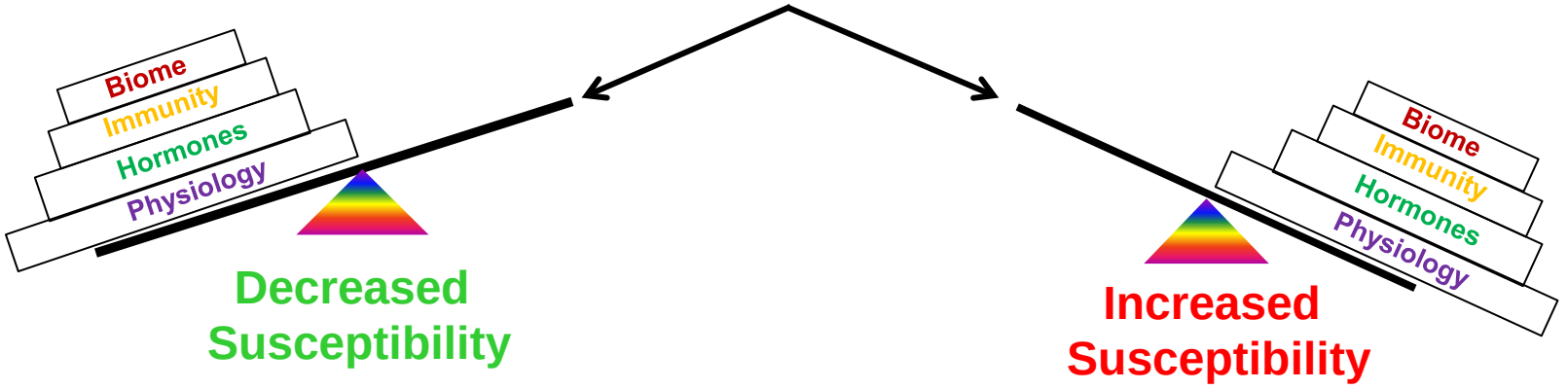
Objectives

- How might contraceptive hormones impact HIV risk?
- Is there evidence for any of these possible mechanisms?
- What are the ‘hormones’ in hormonal contraceptives and how do they differ?
- What are *some* of the research gaps?
- Provide overview of upcoming MTN-030/IPM 041 Phase I PK and safety study of DPV/LNG vaginal rings

HIV susceptibility is controlled by multiple factors that in aggregate determine the overall degree of susceptibility to infection



Endogenous Biological Factors e.g. maturation, hormone cycles , etc.
Exogenous Factors e.g. trauma, STIs, HC, prevention products, drug delivery systems, etc.



National Institute of Allergy and Infectious Diseases

Slide courtesy of J. Turpin, NIAID

What are the hypothetical ways that HC could increase HIV risk?

- Architectural changes in the vaginal or cervical epithelium
  - ~~Thinning or disruption?~~
  - Alterations in tight junctions?
  - Alterations in adhesins or other cell structural proteins/glycoproteins
- Alterations in cellular targets for infection
  - T-cells (CD4 predominantly) and other APC (DCs, monocytes, MΦ)
  - HIV co-receptors (CCR5)
  - Activation state of target cells
- Interference with adaptive and innate immune responses
  - Alterations in soluble responses (chemokines, cytokines, other mediators)
- ~~Alterations in vaginal microbiome~~
- Indirect effects: increased HSV infection
- Direct effects on the virus in the founder population stage of early infection?

What is the evidence for alterations in cellular targets?

- Genital tract lymphocytes and APCs fluctuate with endogenous hormonal change, including pregnancy
- Genital tract lymphocytes and APCs fluctuate with exogenous hormone use:
  - **FRT cells are altered *in vitro* in response to exogenous sex steroid hormone exposure**
  - **CCR5 expression on CD4+ T-cells in cervix and PBMCs may be increased in women using "COCs"**
  - **Alterations in the number of T cells, MΦ, and HLA-DR and CCR5+ T-cells in genital tract tissues following DMPA administration**
  - **Inhibition of normal down-regulation of surface HIV co-receptors on T-cells when activated**

Wira, Nat Rev Immunol 2015
Prakash, J Reprod Immunol 2002

Chandra, AIDS Res Hum Retroviruses 2013
Huijbregts, Endocrinology 2013

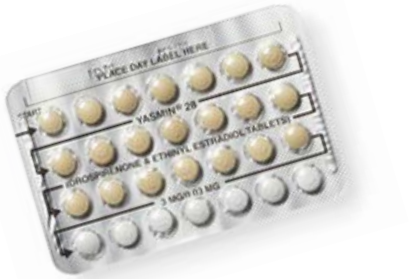
What is the evidence for interference with adaptive and innate immunity?

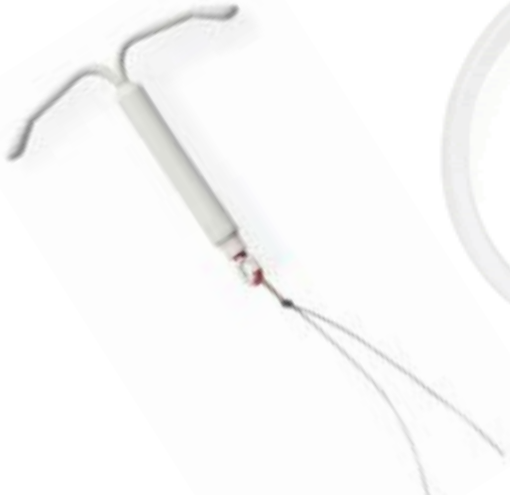
- Progestins differ widely in their steroid receptor selectivity profiles
  - MPA binds GR with an affinity similar to cortisol and acts as agonist
  - Glucocorticoids are widely used as anti-inflammatory/immunosuppressive drugs
- MPA regulates inflammatory genes in endocervical cells *in vitro* vs NET-A
- DMPA blocked IFN production by pDCs in mice and women
- DMPA blocked production of cytokines/chemokines by activated T-cells
- MPA altered innate soluble mediator expression (e.g. SLPI, lactoferrin)
- MPA decreased RANTES (competitive binder of CCR5) *in vitro* yet increased RANTES in women using DMPA

Hapgood, Am J Reprod Immunol 2014
Govender, PLOS One 2014
Huijbregts, Endocrinology 2013

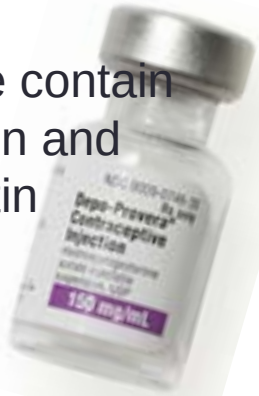
Africander, Contraception 2011
Morrison, J Acquir Immune Defic Syndr 2014
Michel, J Acquir Immune Defic Syndr 2015

Current hormonal contraceptives come in many shapes, doses and formulations





…some contain estrogen and progestin

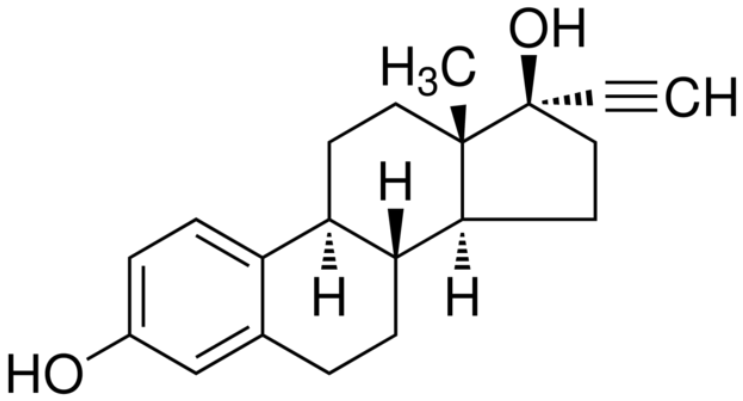


…others only contain progestin only

There is not a lot of variation in the estrogen component

- HC methods can be grouped by ± estrogen
  - Low dose ethinyl estradiol (EE)

- EE is similar to estradiol (E_2)
  - predominant natural estrogen in non-pregnant reproductive age ♀
- The estrogen component is not responsible for the contraceptive efficacy
  - Endometrial stability
  - Improved bleeding patterns

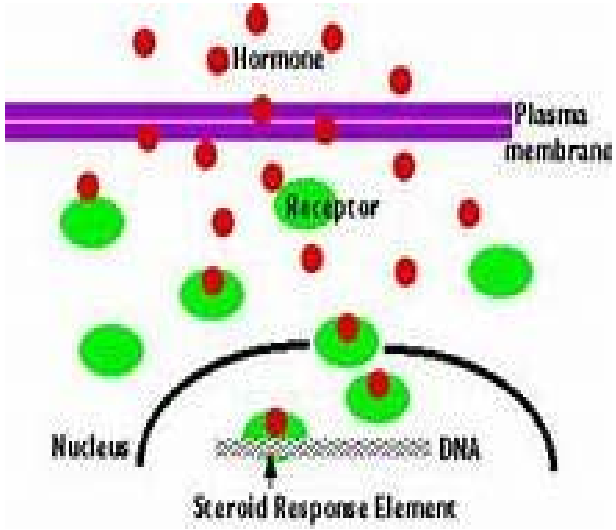


The big variable is the progestin

- Progestogen (induces a secretory endometrium in order to support pregnancy)
  - Natural (progesterone) and synthetic forms (many)
- Progesterone
  - The only natural progestogen
- Progestin
  - All synthetic progestogens
  - MANY varieties
    - Some derived from progesterone (pregnanes)
    - Most derived from testosterone (estranes and gonanes)
    - Few derived from spironolactone
  - The progestin is responsible for efficacy in HC
  - **Impacts many aspects of human physiology**
  - **MANY different binding affinities for PR, AR, GR, MR**

Progestins bind many steroid receptors

- Progesterone
- Androgen
- Glucocorticoid*
- Mineralocorticoid

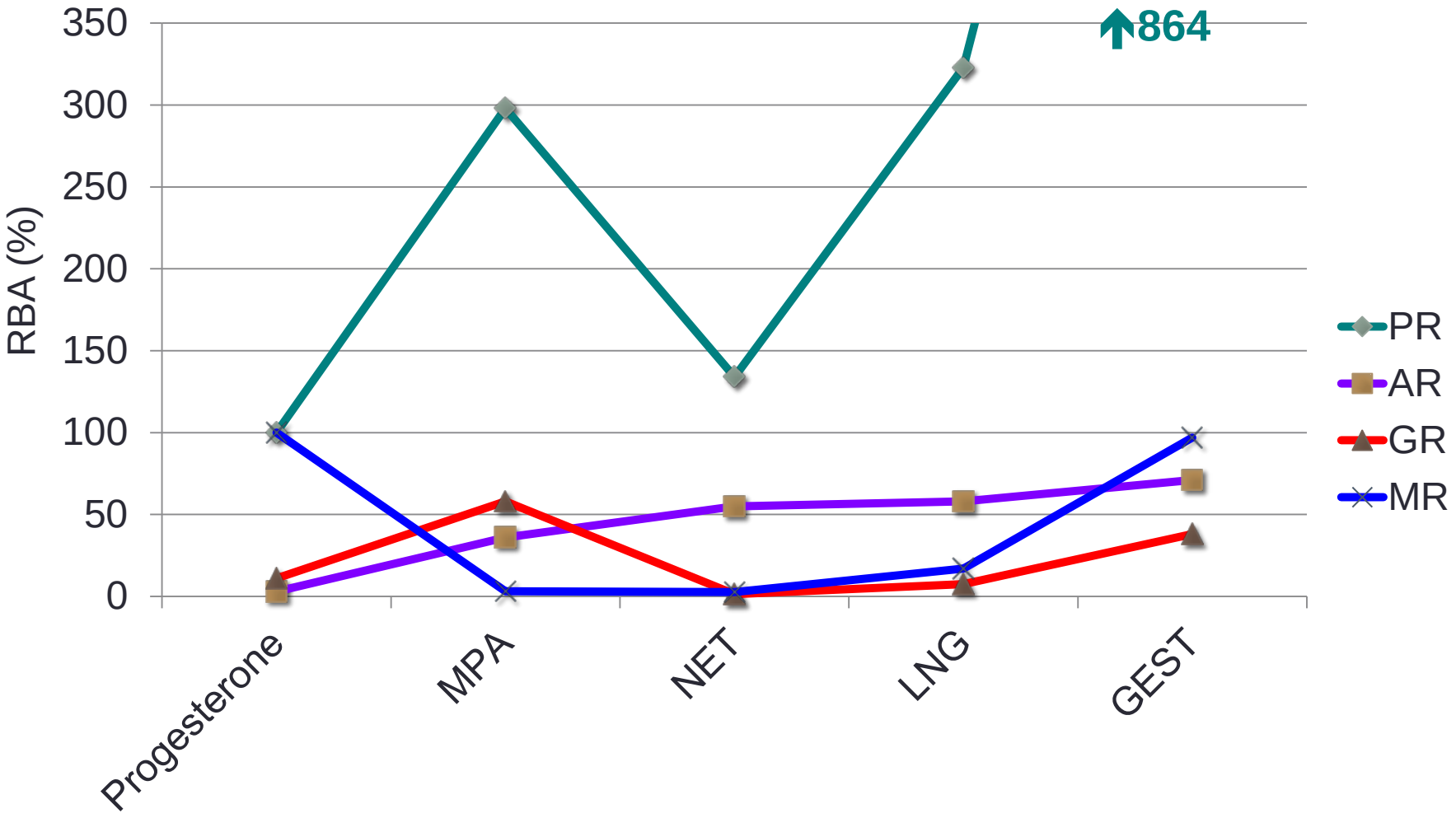


Each progestin has different binding affinities for these receptors—and different impacts on physiology

*GR regulates genes controlling immune response—naturally bound by cortisol so overall effect is immunosuppression:

- Cytosol: blocks binding of pro-inflammatory transcription factors (NFκB and AP-1)
- Nucleus: activating transcription of anti-inflammatory proteins

Each Progestin has Unique Binding Affinities



Stanczyk, Endocrine Reviews 2013

We have a BIG gap

- The study of non-contraceptive effects of HC has been complicated by the sheer diversity of available hormones and delivery routes:
  - Different progestins
    - Different PR, AR, GR, MR binding affinities
    - Different rates of metabolism with different metabolite activities
  - Different delivery routes
  - Different resultant systemic and local tissue concentrations

…yet these methods have generally been grouped together as if they are the same

Some other contraceptive research gaps

- The study of non-contraceptive effects of HC has also been complicated by:
  - Frequent contraceptive switching by women
  - Lack of serum and tissue progestin concentration data to accurately categorize exposure vs outcome
    - Nearly all studies that assess contraceptive use, have done so by self-report

MTN and IPM collaboration on DPV-LNG vaginal ring development

MTN
microbicide trials network

Microbicide
+
Contraceptive

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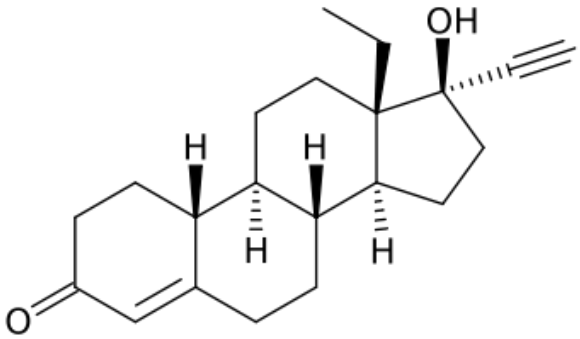
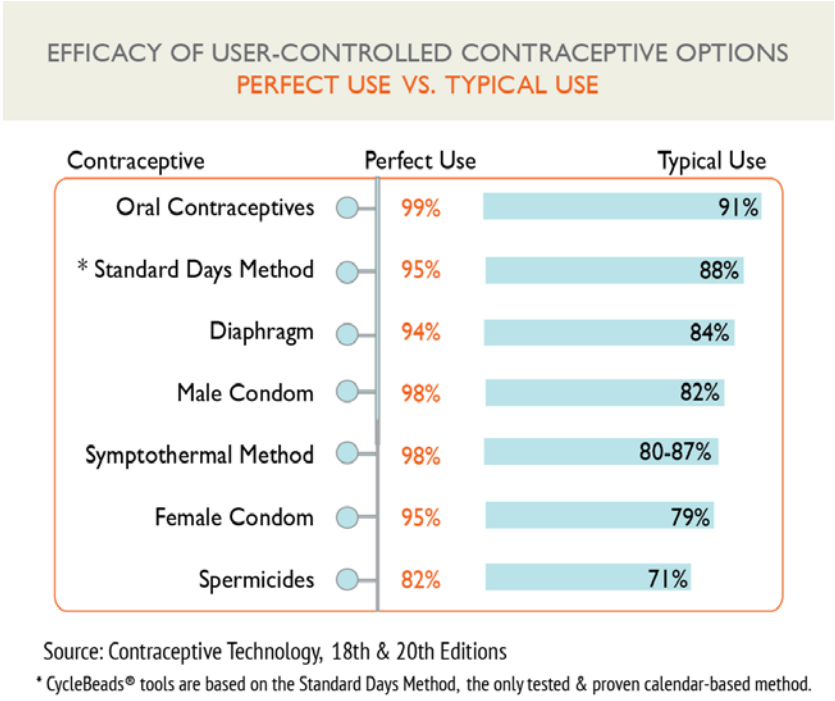
Ring Components: Levonorgestrel

- Contraceptive progestin in widespread use
- Excellent safety profile
- Large dosing range
  - Contraceptive efficacy threshold* ~200 pg/mL
  - LNG implants: ~250-700 pg/mL
  - LNG-based COCs ~1-2 hrs after dosing:
    - Single dose: 2000-3700 pg/mL
    - Steady state: 3300-8700 pg/mL
    - Single 1.5mg dose: up to 22,000 pg/mL



Contraceptive efficacy of low-dose LNG rings

- Efficacy of silicone ring with initial release of 20 µg/day used for 90 days
  - WHO study (n = 1005)
    - Pregnancy rate at 1 year: 3.6 per 100 women (95% CI 2.2-5.0)
  - UK study (n = 1591)
    - Pregnancy rate at 1 year: 5.1 per 100 women (95% CI 3.6-6.6)
    - Pregnancy rate at 2 yrs: 6.5 per 100 women (95% CI 4.4-8.6)



Wide variation in serum [LNG]

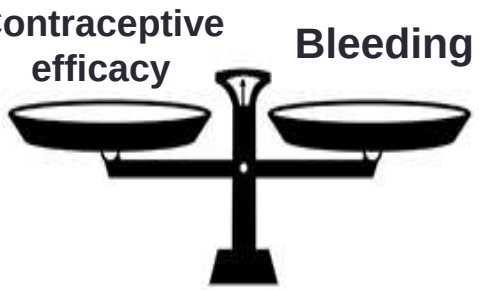
~50% of 30-day cycles were 'normal ovulatory-like' on product

More BTB in anovulatory cycles

Koetsawang Contraception. 1990
Sahota et al. Adv. Contracept. 1999
Landgren et al. Contraception 1982, 1986, 1994

Issues with Levonorgestrel dose

- Contraceptive efficacy vs bleeding



- Understanding vaginal administration
  - PK
  - PD

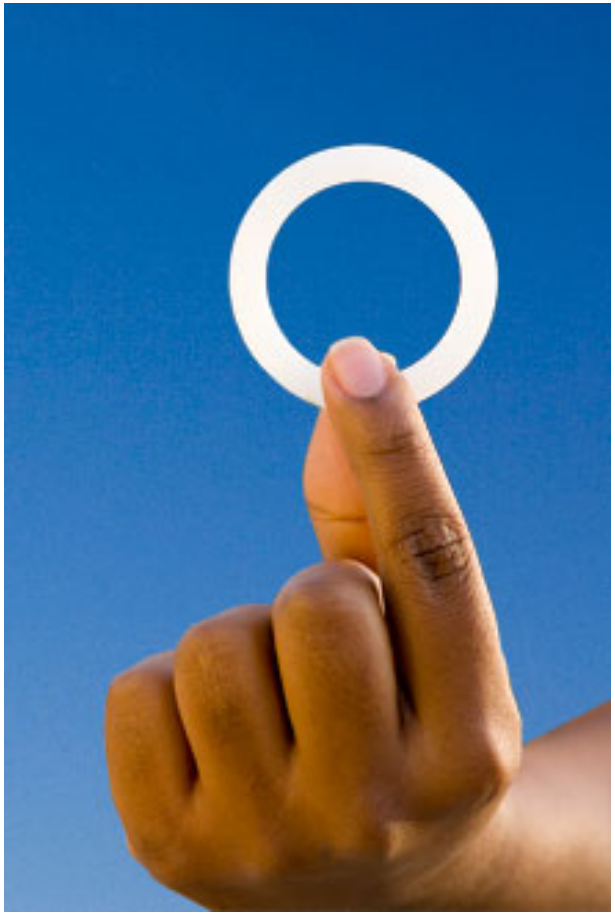
- Understanding MOA
  - Lack of excellent objective tools as surrogates for contraceptive efficacy
    - Ovulation suppression
    - Cervical mucus—measurement variability
    - Endometrial effects?
    - Drug PK/PD with respect to efficacy?

Ring Components: Dapivirine

- NNRTI (binds to and disables the HIV RT enzyme required for viral replication)
- Sixteen clinical safety studies of dapivirine formulated as either vaginal gel or vaginal ring have been conducted to date
  - Excellent safety profile
  - 25mg rings designed for 28-day use currently in Phase III trials
    - Aspire and The Ring Study with 3,476 and 1,950 participants
  - Delivers high concentrations of active drug to vaginal tissue with trace amounts absorbed systemically
  - Highly acceptable and well-tolerated by African women
- Need to increase dose moving from 28-day ring to 90-day ring

Ring structure

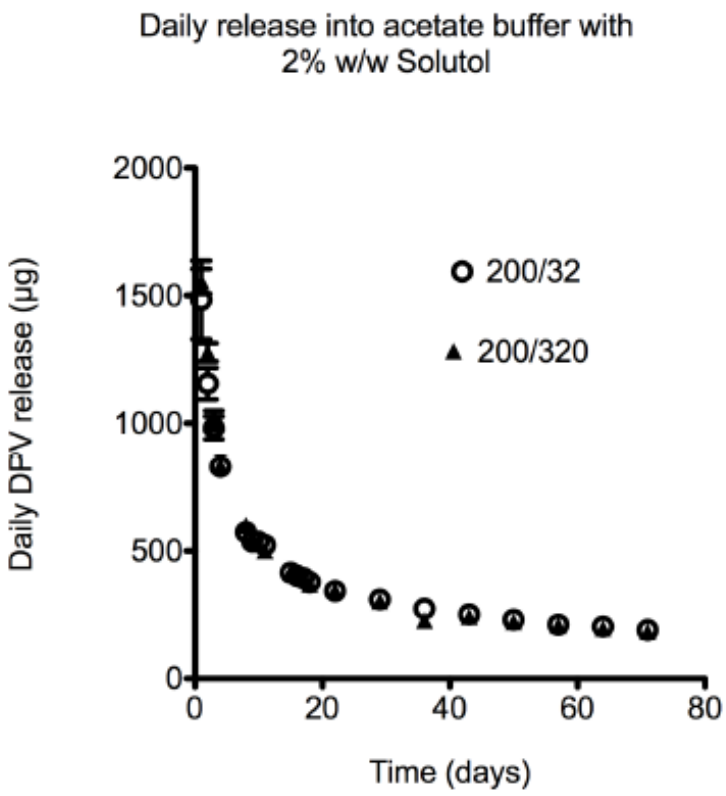
- Matrix ring with same dimensions as dapivirine ring in Phase III trials
- Silicone polymer
  - Platinum-catalyzed, addition cured
- Target stability for at least 36 months in SSA environment
- Goal of 90-day use ring

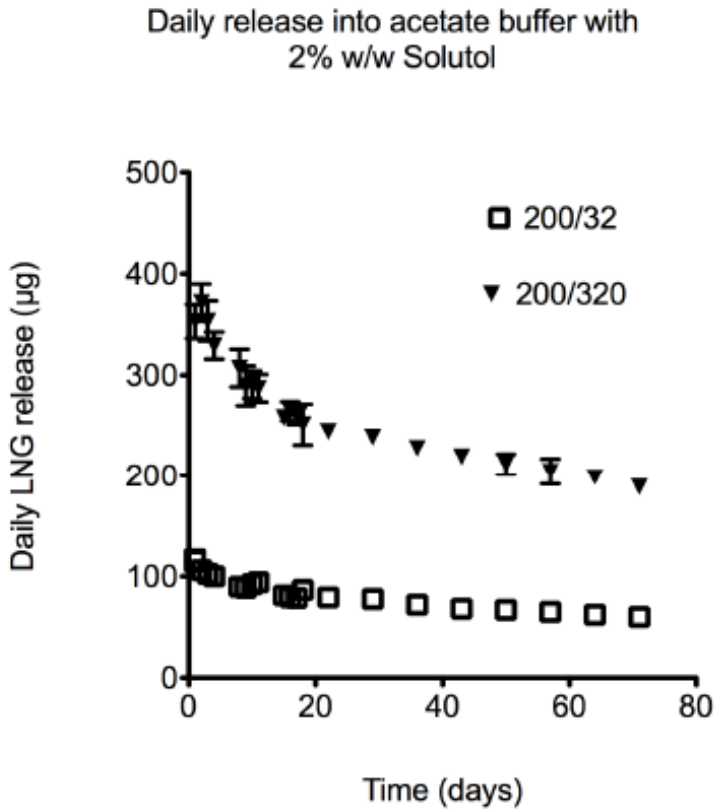


Rings for Study

- DPV 200mg
- DPV 200mg + LNG 32mg
- DPV 200mg + LNG 320mg

Daily release of DAP and LNG *in vitro*





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Courtesy of J. Holt, IPM

Planned study MTN-030/IPM 041

- Phase I (first in humans due to doses)
  - 14-day exposure period
- Randomized, Double-blind
  - 1:1:1 randomization, N=12/arm
- Primary Objectives: PK and Safety
- Secondary Objective: Bleeding profiles
- Exploratory Objectives: Acceptability, Adherence, Vaginal microenvironment

Timeline

- Rings have been manufactured
- Protocol development in final stages
- Enrollment for trial to start Q3 2016

Summary and Conclusions

- Next generation products now in clinical trials: vaginal rings containing antiretrovirals plus LNG
- Progestins differentially interact with a variety of steroid receptors that impact immunity/inflammation
- Many research gaps remain to be answered:
  - Is LNG the best progestin to use?
  - Balancing bleeding/SE vs efficacy
  - PK/PD of progestins by type, delivery method and dose
  - MoA and development of reliable surrogate for contraceptive efficacy

Acknowledgements

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- Jim Turpin
- Joe Romano
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- IPM
- MTN
- CONRAD

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